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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,502	01/03/2005	Christopher M Ward	021911.001110US	2720
20350 7590 07/27/2007 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			EXAMINER NOBLE, MARCIA STEPHENS	
			ART UNIT 1632	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/520,502

Applicant(s)

WARD ET AL.

Examiner

Marcia S. Noble

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 May 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 8-10 and 14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-10, and 14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/10/2007 has been entered.

### ***Status of Claims***

2. Claims 1-6, 8-10, and 14 are pending. Claims 1, 2, 9, and 14 are amended in Applicant's Response, filed 5/10/2007. Claims 1-6, 8-10, and 14 are under consideration.

### ***Specification***

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant requests to hold this requirement in abeyance pending determination of the final language of the claims during prosecution. Request to hold this requirement in abeyance is grant with the objection maintained and the requirement to be addressed when the final claim language is determined.

***Claim Objections***

4. Claim 5 is objected to because of the following informalities: Line 2 of claim 5 recites, "primate porcine". This recitation is grammatically incorrect. A comma is required between "primate" and "porcine". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Scope of Enablement***

5. After consideration of the amendment to the claims and Applicant's arguments the scope of enablement has been modified as follows:

Claims 1-6, 8-10 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A) A method of detecting mammalian embryonic stem cells undergoing differentiation comprising providing a culture of human or mouse ES cells in the presence of LIF, removing the cells from the presence of LIF to initiate differentiation of said ES cells, incubating said ES cells in the presence of an antibody specific for 5T4 antigen wherein said antibody binds to a sub-population of said ES cells, and detecting said cells bound with said antibody, wherein said cells bound with said antibody identify human or mouse ES cells undergoing differentiation;

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B) An in vitro method of isolating mammalian embryonic stem cells undergoing differentiation comprising the method of A) and further comprising isolating said cells bound with said antibody, does not reasonably provide enablement for 1) a method of detecting or isolating any stem cell other than a mammalian stem cell undergoing differentiation; 2) a method of detecting or isolating stem cells wherein the absence of 5T4 antigen expression indicates undifferentiated stem cells; 3) any method of detecting or isolating stem cells undergoing differentiation that uses a means of detection other than a 5T4 antigen antibody; and 4) any method of detecting or separating a differentiated stem cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The critical component and novelty of the instant invention is the finding that 5T4 antigen is found on the surface of some hEC and mES cells early in the process of differentiation following the removal of LIF in vitro, a factor that maintains ES cells in the undifferentiated state. The 5T4 antigen is disclosed as identifying two populations of cells in a sample of ES cells or hEC cells. Those cells that have 5T4 antigen present on their cell surface identified by a 5T4 antibody or express the gene for 5T4 antigen, and those cells that do not. The specification discloses that mES cells, D3, OKO160, MESC, and 129, show no or low levels of 5T4 antigen, but once LIF has been withdrawn the number of 5T4 antigen expressing cells increase following removal of LIF (p. 56, lines 25-30). The specification discloses that the expression patterns of 5T4 antigen are consistent with other reported stem cell markers, such as SSEA. The specification suggests that 5T4 antigen may even serve as a better marker of differentiation status because cells that were 5T4- but SSEA+ were found to have 52% pluripotency as compared the 7% pluripotency for cells positive for both markers. Pluripotency was measured by efficiency of cells to incorporate into chimeric mice (p. 60, lines 14-29). The specification also discloses that hEC with some limited potency adapted to growth on gelatin were strongly positive for 5T4 antigen when sorted by

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FACS suggesting that the cells were undergoing differentiation. In contrast, hEC cells grown on mouse fibroblast were negative for 5T4 antigen (p. 64, lines 22-29), suggesting that they were maintained in the undifferentiated state.

In post-filing art by Applicant, Ward et al disclose that human ES cells lines, HES4 and H1, also express 5T4 antigen on their cell surface during the differentiation process following the removal of LIF (Exp Cell Res (in press), page 2, col 2, par 1, and page 12, col 1, par 1; of record in IDS).

However, the breadth of the claims are not supported by the specification for the following reasons:

1) The claims are drawn to determining the differentiation status or separating any stem cell. As previously discussed in the previous office actions, the breadth of any stem cell encompasses embryonic stem cells and adult stem cells. The specification discloses that 5T4 antigen was detected in all mES cell lines following withdrawal of LIF for three days (p. 56, lines 25-28). Example 3 of the specification teaches that hEC and a human ES cell demonstrate a similar expression profile of 5T4 antigen following LIF removal (p. 66, lines 15-17). In post-filing art, Ward et al more specifically show that hes4 and H1 human ES cell demonstrate a similar expression profile of 5T4 antigen following LIF removal (see abstract). However, the specification does not teach that adult stem cells express 5T4 antigen or that its expression is a measure of differentiation status in adult stem cells.

The art also does not teach that adult stem cells express 5T4 antigen or that its expression is a measure of differentiation status in fetal or adult stem cells. However,

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the art does teach that embryonic stem cells differ from adult stem cells. Unlike embryonic stem cells, adult stem cells can not differentiate into cells of any tissue in the body and are considered unipotent because they can only differentiate along one cell lineage and into cells of a specific tissue (page 1, col 2 to page 2 of Chapter 1 of Stem Cells: Scientific Progress and Future Directions, Department of Health and Human Services. June 2001). The art suggests that adult stem cells comprise precursor or progenitor cells that are intermediate stem cells that are committed along a differentiation pathway and are further along in the differentiation process than embryonic stem cells (page 23 of Chapter 4 of Stem Cells: Scientific Progress and Future Directions, Department of Health and Human Services. June 2001.)

Therefore, since the art suggests that adult stem cells are characteristically different from embryonic stem cells and that they are in a different differentiation status as compared to embryonic stem cells, and the specification and art only teach that 5T4 antigen is expressed early in the differentiation process of mouse and human embryonic stem cells, an artisan would recognize that the nature of 5T4 antigen as a marker of differentiation status in adult stem cells is unknown and that it would require further experimentation to determine first if 5T4 antigen is expressed by adult stem cells and then determine if it is a marker of differentiation status in adult stem cells. This level of experimentation which would be necessary to further confirm and conceptually develop the instant methods applicability to adult stem cells is considered undue experimentation, and therefore the instant method is only enabled for embryonic stem cells.



The scope of enablement further limits the cells to mammalian embryonic stem cells because the art suggests that the nature of differentiation markers expression differs and is variable between different embryonic stem cell lines and therefore should be considered on a cell by cell basis. Ward et al (Exp Cell Res 293:229-238, 2004) demonstrates that independently derived ES cell lines vary significantly in their expression of markers of differentiation and their differentiation rate (p. 229, col 2). Data provided by Ward et al demonstrated that several different mouse ES cells line when cultured in the presence of LIF all express Oct3/4 and Rex-1, which are stem cell specific marker expressed in the undifferentiated stem cell (Figure 1, page 232). These data suggest that when cultured in the presence of LIF all the mES cell lines consistently were maintained in the undifferentiated state. However, when the LIF was removed from culture to initiate differentiation of the mES cells, the levels of expression, the timing of expression, and the specific expression of differentiation markers varied between the mES cell lines (Figure 2, page 233). For example, all the cell lines expressed the TTR differentiation marker except BL/6III cells. However, the E14TG2a only expressed the TTR at low levels and the D3 cells only demonstrated strong levels of expression of the TTR on day 9 following removal of LIF. Furthermore, the D3 cells were the only cells to express the differentiation marker ZG. Therefore, these results demonstrate that within mouse ES cell line when and which differentiation markers will be expressed and if they will be expressed at all is depend upon each mES cell line therefore suggesting that each mouse ES cell line must be considered on a case by case basis..

Therefore given the level of variability of differentiation status marker expression in mES cells lines described in the art, an artisan would recognize that the expression of one differentiation status marker by an ES cell does not predictably translate into the same expression profiles into another ES cell line. Therefore, an artisan would need to do further empirical experimentation to determine if first if 5T4 antigen is expressed by other ES cells lines in other species of non-mammals as the claims encompass and then determine if 5T4 antigen is serving as a marker of differentiation status. This level of experimentation to overcome the unpredictability described in the art would be considered undue.

The scope of enablement was broadened to include mammalian cells because upon further consideration of the data disclosed in the specification and post-filing art, enough examples of mouse and human ES cells were provided to suggest that a trend for 5T4 antigen expression as a marker for differentiation in mouse and human ES cells existed. However, given the unpredictability in the art, these two examples of species do not enable the full breadth of any species of animal.

Therefore given the rudimentary nature of 5T4 antigen expression as a marker of differentiation, the unpredictabilities of differentiation status marker expression in different cell lines, and the amount of undue experimentation that would be necessary, the instant claims are only enabled for mouse and human ES cells and are not enabled for the bread of any stem cell from any species.

2) The instant claims specify wherein the absence of 5T4 antigen expression indicates an undifferentiated stem cell (claim 2). However, the art suggests that the lack

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of a differentiation marker does not necessary indicate that the stem cells are not undergoing differentiation or is not a differentiated cell. Again referring to Ward et al (Exp Cell Res 293:229-238, 2004), Figure 2 demonstrates that BL/6III ES cells are not expressing the differentiation marker TTR, whereas the 4 other ES cells do express TTR when LIF is removed. However, the BL/6III are expressing other marker of differentiation such as NF-68 and fgf-5. These results indicate that BL/6III cells are undergoing differentiation however these cells do not express all the same differentiation markers as other stem cell. Therefore, these results suggest that the absence of a stem cell marker does not necessarily indicate an undifferentiated stem cell as is claimed for the 5T4 antigen. Therefore, the instant invention is not enabled for an embodiment wherein the absence of 5T4 antigen indicates an undifferentiated stem cell as claimed.

3) The breadth of the claims encompasses a method of detecting or separating stem cells using any means of detecting expression of 5T4 antigen. This breadth encompasses detecting mRNA levels of 5T4 antigen and demonstrating differentiation status or isolating cells that express 5T4 antigen mRNA. However, Ward et al (Exp Cell Res in press 2006, of record in the IDS) suggests that 5T4 antigen expression does not predictably measure differentiation status of stem cells. Ward et al state that 5T4 transcripts were absent from undifferentiated H1 ES cells and detected in the differentiated population. In contrast, HES4 cell have readily detectable transcripts for 5T4 antigen in the undifferentiated and differentiated populations (p. 4, col 2, par 2). Ward et al further state (p. 4, col 4 par 2), "This is in agreement with our studies in

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mouse ES cells where cell surface localization of the 5T4 antigen is the critical demonstrator of differentiation rather than transcript levels.”

Therefore, because the art suggests that 5T4 antigen transcripts do not predictably indicate differentiation status and further suggests that cells surface expression of the 5T4 antigen is the critical indicator of the differentiation status, the instant method is not enabled for method that do not use cell surface expression of the 5T4 antigen as their means of detecting differentiation status. Furthermore, the use of a mammalian 5T4 antigen antibody is the only means by 5T4 antigen cell surface expression is detected in the specification. Therefore the instant invention is only enabled for detection of 5T4 antigen cell surface expression by a 5T4 antigen antibody.

4) The claims encompass detecting or separating “differentiated stem cells” (see independent claims 2, 8, 9, and 14). However, the specification teaches that the 5T4 antigen is being expressed early in the process of differentiation but does not teach that 5T4 antigen is detecting stem cells that have completed the process of differentiation or are differentiated. The state of the art also suggests that stem cells by the definition are not differentiated (page 1 of Chapter 1 of Stem Cells: Scientific Progress and Future Directions, Department of Health and Human Services, June 2001). Therefore, because stem cells by definition can not be differentiated and the method disclosed by the specification is a method of detecting stem cells undergoing differentiation in the early stages of the differentiation process, an artisan would not know how to use the instant method to detect or isolate differentiated stem cells as claimed. Therefore, the

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instant invention is only enabled for a method of detecting stem cells that are undergoing the process of differentiation.

Applicant traversed the original enablement rejection on the grounds that the Examiner has not provided a prima facie case of enablement and that Examiner does not fundamentally understand the claimed invention.

Applicant's arguments are not found persuasive because these assertions in themselves do not demonstrate a lack of prima facie case of enablement and a lack of understanding the claimed invention. However, given these concerns of Applicant, Examiner has modified and restated the lack of enablement rejection to try and clarify the issues of enablement for Applicant using references from the art to support the issues of enablement.

Therefore, because the amendments to the claims and the arguments provided by Applicant do not overcome the enablement issues made of record and clarified in the above modified scope of enablement rejection, the instant rejection is maintained.

### ***112, 2<sup>nd</sup> Paragraph Rejection***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The rejection of claims 2 under 35 U.S.C. 112, second paragraph, as being indefinite in its recitation of "low or negligible level", is withdrawn.

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Applicant removed this recitation from the claim, and therefore the rejection is withdrawn.

7. The rejection of claims 1-6 and 14 under 35 U.S.C. 112, second paragraph, as being indefinite for their recitation of "reflects", is withdrawn.

The amendment to the claims removed this recitation. Therefore, the rejection is withdrawn.

8. Claims 2-6, 8-10, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 8, 9, and 14 recite, "differentiated stem cells". The metes and bound of this recitation are indefinite because by definition a stem cell is not differentiated. Therefore, it is not apparent whether this recitation is meant to encompass stem cells or differentiated cells.

Claims 2-6 and 10 depend from claims 2 and 9, respectively, which have been deemed indefinite. Therefore these dependent claims are also rendered indefinite.

Claim 9 recites the limitation "the cells" in step c. There is insufficient antecedent basis for this limitation in the claim. This recitation lacks antecedent basis because it is not apparent from the claims if isolating "the cells" in step c refers to the undifferentiated stem cells or the differentiated stem cells.

Claim 10 depends from claim 9 and therefore also lack antecedent basis.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 14 broadly comprises "use of an antibody" but does not provide any step or manner by which the antibody is to be used.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The rejection of claims 1, 3, 8, and 14 under 35 U.S.C. 102(b) as being anticipated by Southall et al (Br J Cancer 61:89-95, 1990), is withdrawn.

Applicant traversed this rejection by asserting that the claims encompass the expression of 5T4 antigen which identifies differentiated stem cells whereas the opposite occurs in Southall et al who reports that expression of 5T4 antigen in carcinoma cells indicate an undifferentiated cell.

This argument is found persuasive because Southall et al does demonstrate a different effect associated with 5T4 antigen and the specification only encompasses stem cells that are not cancer cells. Therefore, the rejection is withdrawn.


10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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